Upgrading antibiotic use within a class: Tradeoff between resistance and treatment success

Upgrading antibiotic use within a class: Tradeoff between resistance and treatment success

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Increasing resistance to antibiotics creates the need for prudent antibiotic use. When resistance to various antibiotics within a class is driven by stepwise accumulation of mutations, a dilemma may exist in regard to replacing an antibiotic that is losing effectiveness due to resistance with a new drug within the same class. Such replacement may enhance treatment success in the short term but promote the spread of highly resistant strains. We used mathematical models to quantify the tradeoff between minimizing treatment failures (by switching early) and minimizing the proliferation of the highly resistant strain (by delaying the switch). Numerical simulations were applied to investigate the cumulative prevalence of the highly resistant strain (*Resistance*) and the cumulative number of treatment failures (*Failure*) that resulted from following different antibiotic use policies. Whereas never switching to the new drug always minimizes *Resistance* and maximizes *Failure*, immediate switching usually maximizes *Resistance* and minimizes *Failure*. Thus, in most circumstances, there is a strict tradeoff in which early use of the new drug enhances treatment effectiveness while hastening the rise of high-level resistance. This tradeoff is most acute when acquired resistance is rare and the highly resistant strain is readily transmissible. However, exceptions occur when use of the new drug frequently leads to acquired resistance and when the highly resistant strain has substantial "fitness cost"; these circumstances tend to favor an immediate switch. We discuss the implications of these considerations in regard to antibiotic choices for *Streptococcus pneumoniae*.

antibiotic resistance | fluoroquinolones | mathematical models | optimization

Antimicrobial resistance is a growing threat to public health in both developed and developing countries (1, 2). The emergence and spread of resistance demonstrates the ecological and evolutionary response of bacterial species to the selection pressure imposed by widespread use of antibiotics (3). In a variety of species, the discovery and widespread clinical use of an antimicrobial drug has been followed by the emergence of resistant strains, frequently creating the need for still newer drugs. This "arms race" between bacterial resistance and antimicrobial innovations presents a strategic question: When should a drug that is losing effectiveness due to rising resistance be replaced with a novel drug in the same or different class (e.g., replacing gentamicin with amikacin in hospital settings) (4, 5)? Antibiotic policies in general, and specifically the decision concerning a change in prescribing practices, have two objectives: (*i*) to improve treatment effectiveness for the current population and (*ii*) to prevent the emergence of higher-level resistance in the future.

In the case of two antibiotics with distinct mechanisms of action, theoretical and empirical research supports the merits of combination therapy to both prevent treatment failure in individuals and control antimicrobial resistance at the population level; in other words, the same policy may satisfy both objectives (6–8). In other cases, the two objectives may be in conflict. For a bacterial pathogen that is increasingly resistant to a widely prescribed agent, promoting the use of a novel drug with activity against the resistant strains leads to fewer treatment failures and delivers benefits to current patients (4, 9). On the other hand, switching to a new drug imposes a selective pressure in favor of strains that are resistant to even the new antibiotic (10–12). Thus, we may expect that such a switch achieves the first objective at the expense of the second. Specifically, when considering two antibiotics within the same therapeutic class, high-level resistance is often conferred through sequential accumulation of chromosomal mutations or acquisition of new genetic material (8). This stepwise mechanism makes combination therapy or cycling of two antibiotics of the same class impractical. For example, resistance to fluoroquinolones in *Streptococcus pneumoniae* is mediated by chromosomal changes on two genes: DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) (13). The first generation of fluoroquinolones, such as ofloxacin and ciprofloxacin, preferentially targets one of the two loci. Since 1994, however, a number of newer "dual-activity" fluoroquinolones, including levofloxacin (the second generation) and gatifloxacin and moxifloxacin (the third generation) (14), that demonstrate more comparable activity against both genes, have been developed. Because at least two mutations are usually required in order to confer a biologically significant resistance to these newer agents, the likelihood for a resistant strain to emerge during treatment of a fully susceptible infection is much lower (15–17). On the other hand, a strain already resistant to an "old" fluoroquinolone is only one mutation away from becoming resistant to the newer drugs, making selection of a fully resistant mutant more likely from such "precursor" strains.

In the presence of such a stepwise mechanism, does treatment success for today's patients still inevitably lead to faster selection of resistance? It may do so, as argued above; however, a contrasting argument runs as follows: Because strains resistant to the older fluoroquinolones are the genetic precursors to higher-level resistance, early upgrade to the new agents could "block" the pathway toward selecting for highly resistant strains (18). Early use of the newer drugs also presents immediate benefits to patients. Therefore, an immediate switch to the more active drugs could achieve both better outcomes today and slower evolution of resistance tomorrow.

In upgrading the drug of choice for empiric therapy, determining whether the two objectives are consistent or in conflict requires a specific quantitative model. We evaluate this possible tradeoff by using a mathematical model to simulate the dynamics of commensal bacteria possessing a stepwise genetic basis for resistance. We consider the transmission dynamics of three strains: (*i*) drug-sensitive, (*ii*) resistant to the old drug but sensitive to the new drug, and (*iii*) resistant to both drugs. We ask how the timing of a population-wide switch from the old drug to the new drug affects two objectives. The first objective is to minimize the cumulative prevalence of highly resistant strains over time and is defined mathematically by using a *Resistance* function. The second objective

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Abbreviation: MIC, minimal inhibitory concentration.

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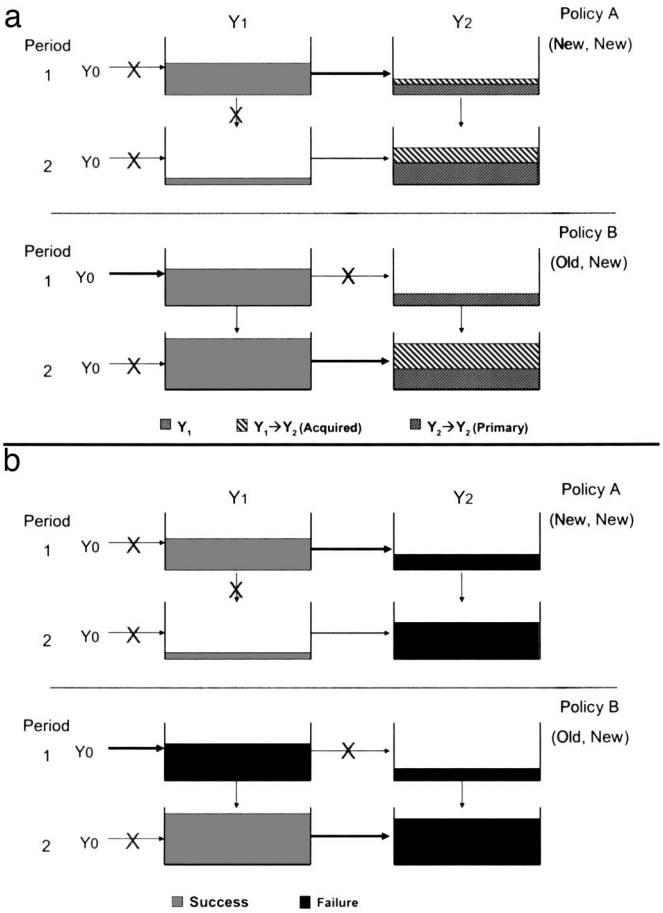

Fig. 1. Qualitative description of the dynamics of the low-level resistant strain (Y_1) and the highly resistant strain (Y_2) under two different antibiotic-switching policies. The contents of each "barrel" represent the amount and composition of each strain, by mechanisms of emergence (acquired vs. primary). Xs indicate inhibition or blockage. Policy A (immediate switch) uses the new drug in both periods 1 and 2, whereas policy B (delayed switch) uses the old drug in period 1 and switches to the new drug at the beginning of period 2. The objective function *Resistance* (*a*) accumulates the presence of Y_2 over both periods, whereas *Failure* (*b*) counts failed treatment episodes among treated hosts. (*b*) is the same as (*a*), only recoded to indicate treatment outcomes.

is to minimize the cumulative number of ineffective treatment episodes (defined by using a *Failure* function). We examine whether the two objectives are at all times incompatible, that is, whether an early switch to the new drug will decrease *Failure* and inevitably increase *Resistance* or, on the other hand, whether delayed switch will slow the rise of *Resistance* at the cost of more *Failure* over time. Previous models of antibiotic policies have mostly focused on either curbing the overall presence of resistant bacteria (19–22) or minimizing the total burden of infection (23) by managing two or more classes of drugs. To the best of our knowledge, no prior study has highlighted the possible conflict in regard to updating antibiotic formularies within the same class.

Results

Qualitative Results. Fig. 1 illustrates the effect of a population-wide switch to the new drug on each of the two outcomes: *Resistance* and *Failure*. Early adoption of the new drug (policy A) allows more time for the highly resistant strain, Y_2, to spread (i.e., "primary resistance") with suppressed competition from the less resistant strains: the wild-type, Y_0, and the low-level resistant strain, Y_1. In contrast, delaying the switch (policy B) allows more accumulation of Y_1 from treating Y_0 hosts with the old drug and from permitting the spread of Y_1 without hindrance from the new drug. Because Y_1 is a precursor of Y_2, more Y_1 in the population leads to the emergence of more Y_2 ("acquired resistance") once the switch is made at a later time (as shown in Fig. 1*a*). If the primary mechanism is more prominent than the acquired mechanism, then an immediate switch will lead to more cumulative presence of Y_2 (higher *Resistance*) than a delayed switch. On the other hand, if the acquired mechanism dominates, a delayed switch could result in rapid accumulation of Y_2 after the switch and eventually lead to more resistance.

Contributions of ineffective patient–drug encounters to the *Failure* function are driven by similar counterbalancing effects (Fig. 1*b*). The most apparent benefit of instant switching is that of avoiding treatment failures among treated Y_1 hosts. However, treatment failures may later begin to accumulate rapidly as a result of the rise of the highly resistant strain. If the initial prevalence of Y_1 is high, the immediate benefit of switching to the new drug will be quite large. However, if early switching to the new drug greatly fosters the emergence of Y_2, mainly from primary resistance (transmission), the cumulative ineffective treatment episodes can surge after the switch and, eventually, offset its early benefit. These observations indicate that the tradeoff between the consequences depends on the relative magnitude of multiple countervailing effects of an antibiotic switching policy on population dynamics.

Quantitative Results: Numerical Simulations. On the basis of 2,000 random parameter sets (summarized in Table 1) chosen from our structured sampling process, the switch timings that result in the highest and lowest values of *Resistance* and *Failure* functions are summarized in Table 2 and as follows.

***Result 1: Never switching to the new drug always minimizes* Resistance**. In all 2,000 sample scenarios, the policy to minimize *Resistance* is to never use the new drug (Table 2). Fig. 3, which is published as supporting information on the PNAS web site, illustrates typical trajectories of such scenario. We note that such a policy, although theoretically possible, is unlikely in practice. Because the use of the novel drug will always be beneficial for at least some patients, intentionally withholding a better (and assumedly safe and affordable) drug is unrealistic. Any feasible strategy to designate its best use, even with very restricted use, will lead to some selection pressure for the development of resistance.

Result 2: Immediate switching maximizes* Resistance *in most, but not all, scenarios. Immediate switching results in the greatest *Resistance* in 1,767 of 2,000 scenarios. Immediately after the switch, the use of the new drug curbs the ascent of Y_1 while promoting Y_2. In these cases, the earlier the switch the greater the selection pressure for the highly resistant strain over time (e.g., Fig. 3).

Result 3: Delayed switching maximizes* Resistance *in certain scenarios. Immediate switching did not maximize *Resistance* in 233 (11.65%) of 2,000 scenarios. In these less typical scenarios, the increase in Y_2 after a delayed switch is greater than that after an immediate switch because delayed switch produces a larger pool of the Y_2 precursor, Y_1, and subsequently leads to rapid appearance of Y_2 when the switch takes place (e.g., Fig. 4, which is published as supporting information on the PNAS web site).

***Result 4: Never switching always results in the most* Failure**. Because (by assumption) Y_1 is more prevalent than Y_2 at baseline and has a lower "fitness cost," never replacing the old drug leads to more initial failures and exacerbates the problem by continuing selection to increase the prevalence of Y_1 (e.g., Fig. 5, which is published as supporting information on the PNAS web site).

Result 5: Immediate switching minimizes* Failure *in most, but not all, scenarios. *Failure* is minimized by immediate switching in 1,933 (96.65%) of 2,000 scenarios. In these more typical scenarios, the benefit of an immediate switch by effectively treating Y_1 strains outweighs the cost of promoting Y_2.

Result 6: Delayed switching minimizes* Failure *in a small number of scenarios. In 67 (3.35%) of 2,000 scenarios, delayed switching results in less failure than immediate switching. This result occurs when the

Table 1. Summary of parameter sampling ranges, constraining conditions, and resulting 2,000 parameter sets

Symbol	Variable	Range	Rationale	Final mean (range)
X(0)	Proportion of population with no carriage (X) at time 0	0.5–1	Prevalence of *S. pneumoniae* from surveillance (51)	0.7469 (0.5–0.9998)
f_1	Relative fitness in transmissibility of Y_1 (vs. Y_0)	0.5–1	Unknown in humans (37)	0.9756 (0.9357–1)
f_2	Relative fitness in transmissibility of Y_2 (vs. Y_0)	$f_1(0.5–1)^\dagger$	Unknown in humans (37)	0.9527 (0.8788–0.9989)
e_1	Probability of transition $Y_0 \rightarrow Y_1$ when treated with the old drug	$1e^{-6}$–$1e^{-1}$*	Treatment failure rate (24)	0.0086 ($1.02e^{-6}$–0.01)
e_{12}	Probability of transition $Y_1 \rightarrow Y_2$ when treated with the new drug	$1e^{-6}$–$1e^{-1}$*	Treatment failure rate (24)	0.0094 ($1e^{-6}$–0.099)
P	Proportion of population receiving treatment of this class	0.005–0.2	Prescription rates in U.S. and Hong Kong (52–54)	0.1481 (0.012–0.2)
$Y_1(0)$	Initial proportion Y_1 among all carriers	0.01–0.1	Uncertain (24)	0.0562 (0.01–0.1)
$Y_2(0)$	Initial proportion Y_2 among all carriers	$Y_1(0)\cdot(0.01–1)^\dagger$	Uncertain (24)	0.0274 (0.0002–0.0987)
r	Yearly rate of clearance of carriage in the absence of treatment	2.89 (constant)	Reciprocal of the duration (≈18 wk) of carriage (55)	2.89 (2.89–2.89)
β_0	Transmission rate of drug-sensitive strain (Y_0)	—	Calculated by assuming approximate equilibrium: $1/X = \beta_0/r$ (48)	4.022 (2.8907–5.7785)
T	Time frame	50 (constant)	Sufficiently larger than $1/r$	50

*e_{01} and e_{12} are sampled from log-uniform distributions, thus the exponent is uniformly distributed.
†Sampling for multipliers <1 to constrain $f_1 \geq f_2$ and $Y_1(0) \geq Y_2(0)$. The multipliers are uniformly distributed between the ranges indicated.

rapid escalation of Y_2 after the switch outweighs the benefit of eliminating treatment failures from treated Y_1 hosts (e.g., Fig. 6, which is published as supporting information on the PNAS web site).

Determinants of Atypical Results. We compared parameter sets that led to the "typical" results described in the previous section with sets that generated "atypical" results (results 3 and 6 in the previous section), as summarized in Table 3.

***When delayed switching maximizes* Resistance.** Based on our qualitative analysis of the system, we found that delaying switching will maximize *Resistance* (result 3, as opposed to the more common result 2 in which immediate switching maximizes *Resistance*) when acquisition of high-level resistance during treatment (the $Y_1 \rightarrow Y_2$ transiton) is the dominant process in producing highly resistant strains. This result occurs when the delay leads to a large increase in Y_1 and when the new drug selects for Y_2 easily from this enlarged pool of Y_1. Among the atypical scenarios ($N = 233$), parameters involved in the acquired mechanism for resistance [i.e., e_{12}, P, and $Y_1(0)$] have means significantly higher than among the typical scenarios. Specifically, e_{12} represents the likelihood of this selection and is shown to best differentiate an atypical scenario from a typical one (C-statistic = 0.924). In contrast, acquisition of Y_2 through transmission (primary resistance) is less important in these scenarios, because few Y_2 are present at the start or because the Y_2 strain has low transmissibility (low relative fitness). In other words, in settings where the highly resistant strain transmits poorly but can be readily selected for among hosts with first-step mutants, it might be beneficial to begin using the new drug early, even for the purpose of preventing high-level resistance from emerging.

Table 2. Frequencies of drug policies that minimize or maximize *Resistance* and *Failure*, based on the 2,000 sampled parameter sets

	Resistance		*Failure*	
Drug-switching policy*	Best *N* (%)	Worst *N* (%)	Best *N* (%)	Worst *N* (%)
Never switch	2,000 (100)	—	—	2,000 (100)
Delayed switch	—	233 (11.65)	67 (3.35)	—
Immediate switch	—	1,767 (88.35)	1,933 (96.65)	—

*Never switch, use the old drug throughout the entire 50-year time frame; Delayed switch, start from using the old drug, then switch to the new drug sometime between time 0 and time 5; Immediate switch, switch from the old drug to the new drug at time 0.

***When immediate switching increases* Failure.** According to our qualitative analysis, immediate switching could increase *Failure* (result 6) when the increased transmission of Y_2 due to the switch outweighs the early improvement in the outcome of treatment. Larger values of f_2 and $Y_2(0)$ among the atypical *Failure* scenarios reflect this point because more, fitter Y_2 strains increase the opportunity for Y_2 transmission after the switch. Both parameters are good predictors of such scenarios (C-statistic = 0.882 and 0.707, respectively). Interestingly, a higher level of use of drugs from this class (P) correlates with the occurrence of both atypical *Failure* results and atypical *Resistance* results. Because a large P indicates both a high rate of using the old drug before the switch and high rate of using the new drug after the switch, its net effect on the balance of acquired vs. primary mechanism of Y_2 emergence is vague and must, in practice, depend on its combination with other parameters. Finally, note the somewhat counterintuitive observations that the values of f_1 and $Y_1(0)$ are also significantly higher in the atypical scenarios. This result may reflect constraints imposed during our sampling process, in which we select only parameter sets that satisfy $f_1 \geq f_2$ and $Y_1(0) \geq Y_2(0)$.

Sensitivity Analyses on Model Assumptions. Clinical experience with older and newer fluoroquinolones has suggested the need to examine possible deviations from two of our model assumptions. In a handful of cases of fluoroquinolone treatment failure, acquired double-mutants (Y_2) have emerged from patients originally carrying wild-type pneumococcal isolates during therapy with ciprofloxacin or levofloxacin (24). These cases suggest that a potential transition, $Y_0 \rightarrow Y_2$, which was not accounted for in our model, might play a significant role in clinical treatment failures. In addition, because the minimal inhibitory concentration (MIC) of bacterial strains is continuous and the first-step mutation (Y_1) often does not result in sufficient MIC increase to confer clinically meaningful resistance to the old drugs (e.g., ciprofloxacin), the old drug may also select for highly resistant strains among treated carriers of the first-step mutant, i.e., the $Y_1 \rightarrow Y_2$ transition during therapy with the old drug (24).

We examined the effect on our main results of allowing the occurrence of the above two transitions. Results are presented in Table 4, which is published as supporting information on the PNAS web site. In general, the more frequently these transitions take place, the more the highly resistant strain is promoted by the old drug and the more favorable immediate switching becomes for the *Resistance* objective (it was already favorable for the *Failure* objective). This finding is particularly true if Y_2 emerges frequently during treatment from carriers of the drug-sensitive strain ($Y_0 \rightarrow Y_2$).

Table 3. Parameter distribution by optimization result types and single-parameter C-statistics

Parameter	Highest *Resistance**			Lowest *Failure*†		
	Typical (N = 1,767)	Atypical (N = 233)	C-statistic‡	Typical (N = 1,933)	Atypical (N = 67)	C-statistic‡
X(0)	0.751 (0.144)§	0.716 (0.138)§	0.569	0.749 (0.144)¶	0.699 (0.138)¶	0.602
f_1	0.976 (0.016)	0.975 (0.015)	0.513	0.975 (0.015)§	0.996 (0.003)§	0.936
f_2	0.954 (0.024)§	0.943 (0.021)§	0.644	0.952 (0.023)§	0.982 (0.011)§	0.882
e_{01}	0.008 (0.019)¶	0.012 (0.022)¶	0.570	0.009 (0.020)	0.011 (0.019)	0.524
e_{12}	0.005 (0.014)§	0.041 (0.030)§	0.924	0.010 (0.020)	0.008 (0.017)	0.510
P	0.147 (0.041)§	0.160 (0.031)§	0.586	0.147 (0.040)§	0.172 (0.023)§	0.678
$Y_1(0)$	0.057 (0.026)§	0.047 (0.027)§	0.609	0.056 (0.026)	0.063 (0.025)	0.578
$Y_2(0)$	0.029 (0.022)§	0.016 (0.016)§	0.689	0.027 (0.021)§	0.042 (0.022)§	0.707

Typical and atypical results are presented as mean (SD).

*Typical results of highest *Resistance* occur with immediate switch, whereas atypical results occur with delayed switch.

†Typical results of lowest *Failure* occur with immediate switch, whereas atypical results occur with delayed switch.

‡Represents the area under the receiver-operating characteristic curve. A value of 1 indicates that the rank-order of the parameter perfectly discriminates a typical from an atypical result; a value of 0.5 indicates no discriminatory power.

§Statistically significant difference in means at $P = 0.001$.

¶Statistically significant difference in means at $P = 0.01$.

Discussion

In the presence of a genetic hierarchy of resistance levels within an antibiotic class, our study suggests that upgrading within the class presents a nearly inevitable tradeoff between fostering resistance to the new drug and enhancing treatment success. Facing a choice between immediately upgrading and continuing the use of an old drug despite declining efficacy, a decision-maker can choose the former to maximize clinical success but (in general) only at the expense of promoting resistance to the new drug.

Our results show that this tradeoff becomes less stringent when the highly resistant strains have limited ability to transmit (25) and the new drug has a high risk of promoting resistance to itself. In this case, an immediate switch will lead to little transmission of the highly resistant strain, and thus the harm of such a policy can be overcome by avoiding the proliferation of the precursor strain that is only one genetic change away from high-level resistance. Similarly, if the old drug can create acquired resistance during treatment, not only to itself but also to the new drug (as in our sensitivity analyses), early switching also becomes more favorable. On the other hand, if the new drug has a very low risk of selecting for resistance from its precursor strains but is highly transmissible once it is present, then reserving the newer drug until the old drug is no longer effective could be the preferable strategy at the population level.

How might such considerations apply to actual antibiotic–bacterial combinations in current clinical use? Given the context in which the model was developed, we focus on *S. pneumoniae*. First, consider our motivating example: fluoroquinolones. For community-acquired pneumonia, use of newer fluoroquinolones has been suggested as a means of averting treatment failure (18, 26). Our model suggests the risk that this benefit would come at the cost of promoting high-level fluoroquinolone resistance; however, the properties of these agents to date seem to minimize such risk. Although resistance to newer fluoroquinolones has been reported (27), high-level resistance remains largely associated with previous treatment, and there has been only limited evidence of clonal spread of fluoroquinolone-resistant pneumococci (10–13, 28). These observations may imply a considerable fitness cost from acquiring incremental mutations associated with high-level fluoroquinolone resistance, a finding recently confirmed in animal models (28). If such a fitness cost is present and persists despite possible compensatory evolution, then it might be possible to use the new fluoroquinolones for an extended period of time before high-level resistance becomes a problem.

A second example is low- vs. high-level resistance to β-lactams in pneumococci. Susceptibilities to penicillin in pneumococci form a continuum, with MIC ranging from $\approx$0.01 μg/ml to $\geq$8 μg/ml (31). Incremental increases in MIC are conferred by acquisition of resistant alleles of three penicillin-binding protein genes, as well as by other mutational and transformational changes. However, high-dose amoxicillin has been shown to eradicate carriage of intermediately resistant, and even some highly resistant, pneumococci, whereas lower-dose regimens are generally only active against susceptible strains (MIC $<$ 0.1 μg/ml) (32). This situation mirrors the old drug/new drug scenario described in our analysis, with the old drug corresponding to lower doses and the new drug corresponding to higher doses of amoxicillin. We and others (32) have suggested that high amoxicillin doses can maintain effectiveness against, and retard the spread of, low-level resistant strains similar to the Y_1 strains in our model. Our model results also suggest that the use of high doses may facilitate the spread of highly resistant strains. Unlike fluoroquinolone resistance, however, an acquisition of exogenous DNA is required to transform strains from moderately to highly resistant; thus, emergence of a highly resistant strain is rare during treatment with β-lactams. The wide clonal spread of highly resistant strains (33) suggests that these strains are not much compromised in their fitness and are capable of spreading. The existence of fit, highly resistant strains may imply compensatory chromosomal changes (34, 35), because animal studies showed pneumococcal strains as being greatly compromised *in vivo* upon acquisition of high-level resistant alleles (36, 37). These characteristics suggest that, in the case of amoxicillin, the policy that maximizes treatment success (widespread use of higher doses) may unfortunately foster the emergence of higher-level resistance at the population level.

Our results should be interpreted in the context of the following limitations. First, our model considered a simplified scenario. Several factors not included in the model can be influential: population characteristics (e.g., age structure and clustering), vaccines (which may reduce, at least temporarily, the burden of resistance) (38–42), and the availability of drug sensitivity testing in some settings. Second, we did not consider antibiotics of other classes and crossresistance. For example, a high proportion of penicillin-resistant pneumococci also showed reduced susceptibility to fluoroquinolones (29, 43), meaning that use of one antibiotic class may promote resistance to other classes. Third, we constrained our parameter sets to a set of scenarios with very low fitness costs, to ensure that it was possible for high-level resistance to spread. Although there are no quantitative estimates of fitness costs for fluoroquinolone resistance, it seems possible that the costs are higher than the values considered here (36, 37), meaning that the actual probability for using newer fluoroquinolones without exten-

sive spread of high-level resistance could be higher. Fourth, although the deterministic nature of the transmission model may be appropriate for large host populations, the occurrence of a new resistant strain is a stochastic process that was not accounted for. Fifth, we have considered the simple question of when a complete switch from an old drug to a new drug should be undertaken. Additional work (data not shown) suggests that the results hold even in the broader "policy space" by considering partial switching (mixed use of the two drugs), but more complicated policies (e.g., multiple changes in the proportion of new vs. old drug over time) have not been considered. Finally, we assumed that treating Y_1 carriers with the old drug leads to clinical failure in all cases. However, for fluoroquinolones such treatment may sometimes be clinically successful (24). This assumption has pushed our results toward favoring earlier switch.

Recent treatment guidelines include newer fluoroquinolones as an option for initial empiric therapy for community-acquired pneumonia in outpatient settings (18, 44, 45). More specifically, although exact criteria vary, these guidelines recommend the first-line use of these newer agents only for selected patients with elevated clinical risk for carrying drug-resistant *S. pneumoniae*, such as recent antibiotic use or cardiopulmonary disease. In the context of our analysis, switching early to newer drugs to which little resistance exists, but reserving them for use in severe cases, may point to a way out of the dilemma suggested in this article. If the use were kept below a level that limits the population-wide selection of the highly resistant strain (22), then it might be possible to combine a low failure rate for high-risk or the most severe cases (because the new drug is used) with continued suppression of resistance (because the drug is used sparingly). Such a strategy is especially reasonable for a pathogen like *S. pneumoniae*, for which most antibiotic use is for non-life-threatening conditions (e.g., otitis media), and evidence suggests considerable fitness cost to high-level fluoroquinolone resistance (28). The herd immunity exerted from the pneumococcal conjugate vaccine has provided evidence that young children play a key role in the transmission of pneumococci (46). However, most invasive pneumococcal diseases cluster within a subpopulation (i.e., older adults). Reserving newer fluoroquinolones mainly for the elderly, a group less central to the transmission of the organism, may exert less selection pressure on the pneumococcal population while providing considerable therapeutic benefits.

In conclusion, when the degree of resistance against various antimicrobial agents in the same class is conferred in a stepwise fashion, the choice of when to upgrade empiric therapy to a newer agent faces a tradeoff between enhancing efficacy and preventing resistance. This tradeoff is less stringent and favors more immediate upgrade when the highly resistant strains are relatively unfit for transmission and when the acquired resistance occurs frequently under newer agents. A prudent approach to this decision would prioritize use of the newer drug in patients at greatest risk for severe outcomes and limit its use in individuals who contribute most to transmission. Ongoing surveillance for phenotypic and genotypic resistance, as well as periodic attempts to measure fitness burdens on resistant strains, will help to keep such policies responsive to bacterial evolution.

Methods

Mathematical Model. Fig. 2 illustrates our compartmental transmission model and the processes by which antibiotic use affects system dynamics. At any time t, an individual resides in one of the four carriage states: no carriage of any strain (X), colonized with the drug-sensitive strain (Y_0), colonized with the low-level resistant strain (Y_1), or colonized with the high-level resistant strain (Y_2). Noncarriers can be colonized asymptomatically from direct contact with carriers and moved to Y_0, Y_1, or Y_2 at rates proportional to the prevalence and the transmissibility (β_0, β_1, and β_2) of each strain (48). Spontaneous clearance of any carriage occurs at a rate r, assumed equal for all strains.

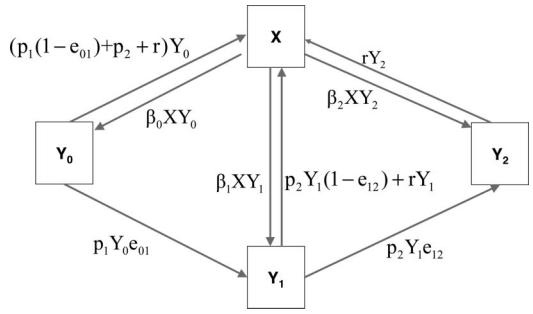

Fig. 2. Structure of the compartmental two-drug/three-strain model. The model describes the transmission dynamics in a closed population. Mathematical expressions quantify the transition rates between indicated carriage states. X represents no carriage; Y_0, Y_1, and Y_2 represent hosts of the drug-sensitive, low-level resistant, and highly resistant strains, respectively. Constants include transmission rates (β_0, β_1, and β_2), probability of selection for Y_1 among Y_0 individuals treated with the old drug (e_{01}), probability of selection for Y_2 among Y_1 individuals treated with the new drug (e_{12}), and rate (r) of carriage clearance in the absence of treatment. The variables p_1 and p_2 represent population-level usage rates of the old and new drugs, respectively.

Both the new drug and the old drug are active against the wild-type strain. When a patient is treated with the old drug, the mean clearance rate of the susceptible strain (Y_0) is enhanced by $p_1(t)$, which represents the incidence of old drug use and the extent to which treatment shortens the duration of carriage. In a few (e_{01}) of these Y_0 individuals treated with the old drug, the low-level resistant strain (Y_1) emerges during treatment. These bacteria are resistant to the old drug but susceptible to the new drug. Use of the new drug accelerates clearance of both the susceptible (Y_0) and the low-level resistant (Y_1) strains by a rate $p_2(t)$, but it also selects for the highly resistant (Y_2) strain to emerge from a proportion (e_{12}) of the treated Y_1 hosts. We assume that the treatment is empiric, without drug sensitivity testing, as in many community-acquired infections; thus, the rate at which an individual receives an antibiotic is assumed to be independent of the drug sensitivity of the strain the individual carries. We also assumed that the transition from Y_0 to Y_2 is negligible (because multiple mutations in the same strain occur at an exceedingly low rate), as is simultaneous carriage of more than one strain. The transitions between these states can be summarized by four ordinary differential equations:

$$\dot{X} = -\beta_0 XY_0 - \beta_1 XY_1 - \beta_2 XY_2 + p_1(t)(1 - e_{01})Y_0 + p_2(t)(1 - e_{12})Y_1 + r(Y_0 + Y_1 + Y_2)$$

$$\dot{Y}_0 = \beta_0 XY_0 - (p_1(t) + p_2(t) + r)Y_0$$

$$\dot{Y}_1 = \beta_1 XY_1 - (p_2(t) + r)Y_1 + p_1(t)e_{01}Y_0$$

$$\dot{Y}_2 = \beta_2 XY_2 - rY_2 + p_2(t)e_{12}Y_1.$$

Antibiotic Switching Policies. Mutually exclusive policy alternatives can be defined by the course of $p_1(t)$ and $p_2(t)$ throughout a time frame substantially longer than the average duration of carriage. As a constraint (because the best way to minimize resistance is to eliminate treatment), we assumed a constant total level of drug use in this class, that is, $p_1(t) + p_2(t)$ for all t. We further restricted our attention to a subset of such functions that reflects a population-wide upgrade on the drug of choice. We define any such policies by parameter τ, such that

$$p_1(t) = \begin{cases} P, & 0 \le t < \tau \\ 0, & t \ge \tau \end{cases}.$$

For any policy, only the old drug is used until time τ, at which point all incident prescriptions of this class are switched to the new drug.

Potential Tradeoff: *Resistance* vs. *Failure*. We defined the first objective, *Resistance*, mathematically as $\int_0^T Y_2(t)dt$ to represent the desire to minimize the cumulative prevalence of the highly resistant strain over the course of T years. The *Failure* objective is defined as the number of individuals being treated with a drug to which their strain is not susceptible, or $\int_0^T [p_1(t)\cdot(Y_1(t) + Y_2(t)) + p_2(t)\cdot Y_2(t)]dt$.

Numerical Simulation and Parameter Sampling. We adopted a numerical simulation approach to explore whether the expected conflict is always present or whether a plausible resolution provided by immediate switching to the new drug may exist. Assuming a 50-year time frame and an 18-week duration of carriage, we searched numerically for four τ values: (*i*) a value that minimizes *Resistance*, (*ii*) a value that maximizes *Resistance*, (*iii*) a value that minimizes *Failure*, and (*iv*) a value that maximizes *Failure*. Had there been a strict conflict between the two objectives, one would anticipate that immediate switching to the new drug would minimize *Failure* and maximize *Resistance*, whereas never using the new drug would minimize *Resistance* at the cost of maximal *Failure*.

Constrained parameter sampling. We designed a random-sampling algorithm to select 2,000 sets of input values to explore the optimal and the worst policies with respect to the two objective functions, within reasonable ranges of parameter values. A sample set consists of eight parameters, each chosen randomly and independently from a uniform distribution. Ranges for these distributions are based on (when available) published literature on commensal bacteria such as *S. pneumoniae* and the prescription trends of fluoroquinolones in developed countries.

We imposed numeric constraints and exclusion criteria during the selection process to ensure the dynamic of this biological system to satisfy the following properties: (*i*) a fitness cost on a strain's transmissibility exists with each step of mutation conferring resistance (35, 49, 50); (*ii*) carriage of any strain is asymptomatic and not associated with noticeable excess mortality, therefore the population size remains constant over time; (*iii*) the low-level resistant strain is more prevalent than the highly resistant strain at time 0; (*iv*) the epidemic of the bacteria is near equilibrium at time 0; and (*v*) when the old drug is in exclusive use, the selection pressure is sufficient to offset the fitness cost of Y_1 relative to Y_0, such that Y_1 can prevail before switching; likewise, Y_2 can prevail after switching. The resulting ranges of the parameters, and corresponding distributions, are summarized in Table 1.

Software. Model construction, simulations, and optimization procedures were programmed in BERKELEY MADONNA (Modeling and Analysis of Dynamic Systems, Version 8.1; R. I. Macey and G. F. Oster, 2001, Univ. of California, Berkeley; www.berkeley-madonna.com) and MATLAB (Student Version 6.5; MathWorks, Natick, MA).

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